



Antibacterial and antifungal properties of resveratrol

Vestergaard, Martin; Ingmer, Hanne

Published in:
International Journal of Antimicrobial Agents

DOI:
[10.1016/j.ijantimicag.2019.02.015](https://doi.org/10.1016/j.ijantimicag.2019.02.015)

Publication date:
2019

Document version
Publisher's PDF, also known as Version of record

Document license:
[CC BY-NC-ND](#)

Citation for published version (APA):
Vestergaard, M., & Ingmer, H. (2019). Antibacterial and antifungal properties of resveratrol. *International Journal of Antimicrobial Agents*, 53(6), 716-723. <https://doi.org/10.1016/j.ijantimicag.2019.02.015>



Review

Antibacterial and antifungal properties of resveratrol

Martin Vestergaard, Hanne Ingmer*

Department of Veterinary and Animal Sciences, Faculty of Health and Medical Sciences, University of Copenhagen, Stigbøjlen 4, DK-1870 Frederiksberg C, Denmark

ARTICLE INFO

Article history:

Received 10 October 2018

Accepted 16 February 2019

Editor: Serhat Unal

Keywords:

Resveratrol

Antimicrobial

Antivirulence

Combination therapy

ATP synthase inhibition

ABSTRACT

Resveratrol is a naturally occurring polyphenolic antioxidant that has received massive attention for its potential health benefits, including anticarcinogenesis, anti-aging and antimicrobial properties. The compound is well tolerated by humans and in recent years has been widely used as a nutraceutical. Its common use makes it interesting to investigate with respect to antimicrobial properties both as a single agent and in combination with conventional antibiotics. Resveratrol displays antimicrobial activity against a surprisingly wide range of bacterial, viral and fungal species. At subinhibitory concentrations, resveratrol can alter bacterial expression of virulence traits leading to reduced toxin production, inhibition of biofilm formation, reduced motility and interference with quorum sensing. In combination with conventional antibiotics, resveratrol enhances the activity of aminoglycosides against *Staphylococcus aureus*, whereas it antagonises the lethal activity of fluoroquinolones against *S. aureus* and *Escherichia coli*. Whilst the antimicrobial properties of the compound have been extensively studied in vitro, little is known about its efficacy in vivo. Nonetheless, following topical application resveratrol has alleviated acne lesions caused by the bacterium *Propionibacterium acnes*. There are currently no in vivo studies addressing its effect in combination with antibiotics, but recent research suggests that there may be a potential for enhancing the antimicrobial efficacy of certain existing antibiotic classes in combination with resveratrol. Given the difficulties associated with introducing new antimicrobial agents to the market, nutraceuticals such as resveratrol may prove to be interesting candidates when searching for solutions for the growing problem of antimicrobial resistance.

© 2019 The Author(s). Published by Elsevier B.V.

This is an open access article under the CC BY-NC-ND license.

<http://creativecommons.org/licenses/by-nc-nd/4.0/>

1. Introduction: beneficial health effects of resveratrol

In recent years, resveratrol has attracted immense attention due to its potential health benefits [1]. One example is known as the 'French paradox', where consumption of red wine, having a high content of resveratrol, has been linked to low mortality caused by cardiovascular diseases in the French population despite their high intake of saturated fat [2,3].

Since then, resveratrol has been extensively studied for a variety of different health-beneficial effects, including, but not limited to, anti-inflammation, anti-carcinogenesis, anti-obesity, anti-diabetes type 2, anti-aging, cardiovascular protection and neuro-protection, which is reviewed elsewhere and therefore is not the focus of this review [4–7]. In addition to the extensive investigations on a multitude of diseases, resveratrol has also been examined for its antimicrobial properties against bacteria, fungi

and viruses. This review concerns the antimicrobial properties of resveratrol, with special emphasis on its antibacterial properties.

2. Natural occurrence and structure of resveratrol

Resveratrol (3,5,4'-trihydroxystilbene) is a naturally occurring polyphenolic antioxidant belonging to the stilbene family. The stilbene family consists of a C6–C2–C6 carbon skeleton (1,2-diphenylethylene), where resveratrol is a hydroxylated derivative (Fig. 1) [8]. Resveratrol is present in numerous plants such as peanuts (*Arachis hypogaea*), blueberries and cranberries (*Vaccinium* spp.), Japanese knotweed (*Polygonum cuspidatum*) a traditional Asian herbal medicine, and most importantly as a natural source for human consumption in grapevines (*Vitis vinifera*) [9]. Being a natural phytoalexin, resveratrol is synthesised de novo by plants in response to damage by fungal attack [10–12] and ultraviolet (UV) irradiation [10]. In a bunch of grapes, resveratrol synthesis is most predominant in the non-infected grapes that surround grapes infected with a fungus to limit the spread of the fungus to healthy grapes, as demonstrated with the fungus *Botrytis cinerea*, the causal

* Corresponding author.

E-mail address: hi@sund.ku.dk (H. Ingmer).

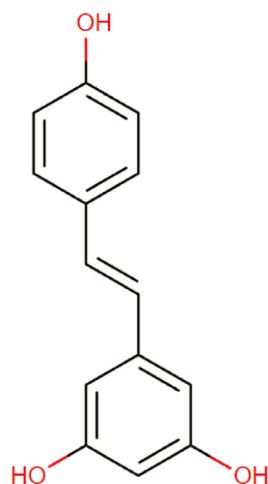


Fig. 1. Structure of resveratrol.

organism of grey mould [13]. Resveratrol exists both in a *cis* and *trans* isomer [4], with the *trans* isomer being the most abundant form in red wine [14] and the most studied due to its greater availability and higher stability [15]. Red wine generally has a greater concentration of resveratrol than white wine [16]. The average red wine contains 1.9 mg/L *trans*-resveratrol but it may reach concentrations up to 14.3 mg/L [14].

3. Antibacterial targets for resveratrol

Resveratrol is a promiscuous molecule that interacts with more than 20 proteins in eukaryotic organisms [17]. As an example, crystallisation complexes have determined a binding site for resveratrol to bovine ATP synthase in the F_1 -domain in a pocket between a β -subunit and the γ -subunit [18]. Conservation of the ATP synthase residues suggests a similar binding pocket for resveratrol in *Escherichia coli* [19]. Resveratrol binds reversibly to ATP synthase, partially inhibiting both ATP hydrolysis and ATP synthesis functions of the ATP synthase in the facultative aerobe *E. coli* [19]. ATP hydrolysis is also inhibited in *Mycobacterium smegmatis* [20], and the metabolic activity of *Arcobacter* spp. is reduced by resveratrol [21]. Supplementation of resveratrol to *E. coli* cells prevents growth on the non-fermentable carbon source succinate and limits growth on fermentable glucose, suggesting that resveratrol inhibits oxidative phosphorylation [19]. As *E. coli* mutants lacking ATP synthase are able to grow in the presence of fermentable carbon sources such as glucose, pyruvate or lactate, ATP synthase cannot be the only target leading to growth inhibition in *E. coli* [22]. Second, resveratrol induces DNA fragmentation and concomitant upregulation of the SOS stress-response regulon in *E. coli*, however inhibition of growth is not directly related to DNA fragmentation and SOS stress-response upregulation [23]. Resveratrol-treated *E. coli* cells are elongated, hence the cell division apparatus is also affected by resveratrol and this occurs via suppression of *ftsZ* expression [23]. FtsZ is a key protein in septum formation during cell division and thus resveratrol is suggested to inhibit FtsZ-mediated septum formation and cell division [23]. Finally, resveratrol treatment has been correlated with membrane damage of cells owing to increased potassium leakage and increased propidium iodide uptake [24]. In contrast, resveratrol-induced membrane damage is not detected for *Staphylococcus aureus* [25].

The pleiotropic effects of resveratrol suggest that multiple targets may exist in bacterial species, however the mechanism for bacterial growth inhibition remains incompletely understood.

4. Antifungal and antibacterial activities of resveratrol

Resveratrol has been extensively studied for its ability to inhibit the growth of bacteria, fungi and viruses. Antiviral activities are reviewed elsewhere and have therefore been omitted from this review [26,27].

4.1. Antifungal activity

Generally, resveratrol displays better antifungal than antibacterial activity, as demonstrated by the minimum inhibitory concentrations (MICs) highlighted in Table 1. For the fungal dermatophytes *Trichophyton mentagrophytes*, *Trichophyton tonsurans*, *Trichophyton rubrum*, *Epidermophyton floccosum* and *Microsporum gypseum*, the inhibitory activity of resveratrol is approximately 25–50 $\mu\text{g/mL}$ [28]. For the fungal species *Candida albicans*, *Saccharomyces cerevisiae* and *Trichosporon beigelii*, the inhibitory activity is 10–20 $\mu\text{g/mL}$ [29], however other studies have not detected antifungal activity against *C. albicans* [30–32]. Resveratrol displays inhibitory activity against the plant pathogen *B. cinerea*, the causal organism of grey mould, where reduced germination of *B. cinerea* conidia and mycelial growth is observed at concentrations of 60–140 $\mu\text{g/mL}$ [11].

4.2. Antibacterial activity

For a limited number of bacterial species, resveratrol inhibits growth at concentrations <100 $\mu\text{g/mL}$, including *Bacillus cereus* (MIC = 50 $\mu\text{g/mL}$) [33], *M. smegmatis* (MIC = 64 $\mu\text{g/mL}$) [34], *Helicobacter pylori* (MIC = 25–50 $\mu\text{g/mL}$) [35–37], *Vibrio cholerae* (MIC = 60 $\mu\text{g/mL}$) [38], *Neisseria gonorrhoeae* (MIC = 75 $\mu\text{g/mL}$) [30], *Campylobacter coli* (MIC = 50 $\mu\text{g/mL}$) [39] and *Arcobacter cryaerophilus* (MIC = 50 $\mu\text{g/mL}$) [21]. The inhibitory activity of resveratrol against *Mycobacterium tuberculosis* is 100 $\mu\text{g/mL}$ [40].

For many bacterial species, resveratrol only displays growth inhibitory activity at concentrations >100 $\mu\text{g/mL}$. Notable Gram-positive pathogens with MICs of approximately 100–200 $\mu\text{g/mL}$ include *S. aureus* [28,30,33,41], *Enterococcus faecalis* [28,33] and *Streptococcus pyogenes* [30]. Several studies have reported lower susceptibilities for several Gram-negative pathogens (MIC > 200 $\mu\text{g/mL}$) compared with Gram-positive pathogens, including *E. coli* [33,41], *Klebsiella pneumoniae* [33], *Salmonella enterica* serovar Typhimurium [33,41] and *Pseudomonas aeruginosa* [28,33,41]. This observation may result from poor penetration of resveratrol across the outer membrane of some Gram-negative bacteria or be the result of active extrusion of resveratrol by efflux pump systems.

Since resveratrol inhibits the ATP synthase in different bacterial species, it remains to be explored whether different requirements for bacterial energy generation partially account for alternating levels of susceptibility to resveratrol.

Some remarkable discrepancies exist between reported MICs, e.g. for *S. aureus* ATCC 25923 the MIC has been reported as 100 $\mu\text{g/mL}$ in one study [33] but as >1000 $\mu\text{g/mL}$ in another study [42]. One explanation for such variation may be differences in growth medium (Mueller–Hinton and Luria–Bertani, respectively), however in general conflicting results on resveratrol susceptibility between studies warrant additional investigation.

4.3. Inactivation of efflux pump systems can increase resveratrol susceptibility

One mechanism that decreases susceptibility to resveratrol is the presence of functional efflux pump systems. In several Gram-negative bacteria the efflux pump AcrAB–TolC actively extrudes numerous antimicrobials [43]. In *E. coli*, a *tolC* mutant displayed four-fold greater susceptibility to resveratrol compared with the

Table 1
Antimicrobial activity of resveratrol against bacteria and fungi.

Organism	Identifier	MIC (µg/mL) ^a	Reference
Gram-positive bacteria			
<i>Bacillus cereus</i>	ATCC 11778	50	[33]
	NCTR-466	1000	[42]
<i>Bacillus megaterium</i>	11561	250	[41]
<i>Staphylococcus aureus</i>	ATCC 25923	100	[33]
	3 clinical isolates	100–200	[33]
	ATCC 29213	171	[28]
	N315	>100	[40]
	8325-4	125	[41]
	RN450	150	[66]
	Clinical isolate	>200	[30]
	Clinical isolate	350	[55]
	ATCC 25923	>1000	[42]
	JE2	256	[25]
	Newman	512	[25]
	COL	128	[25]
<i>Enterococcus faecalis</i>	ATCC 29212	100	[33]
	ATCC 29212	342	[28]
	ATCC 29212	100	[40]
	ATCC 19433	1000	[42]
	ATCC 27274	1000	[42]
	ATCC 29212	128–256	[25]
<i>Enterococcus faecium</i>	D344R	128	[25]
<i>Mycobacterium tuberculosis</i>	H37Rv	100	[40]
<i>Mycobacterium smegmatis</i>	ATCC 700084 (mc ² 155)	64	[34]
<i>Streptococcus pneumoniae</i>	HM145	100	[40]
<i>Streptococcus pyogenes</i>	Clinical isolate	>200	[30]
<i>Propionibacterium acnes</i>	ATCC 25746	180	[45]
	ATCC 29399	186	[45]
	ATCC 33179	196	[45]
	ATCC 6919	>1000	[42]
	LMG16779	200	[44]
<i>Listeria monocytogenes</i>	LMG16780	200	[44]
	LMG13305	200	[44]
	NCTC7973	128	[25]
Gram-negative bacteria			
<i>Escherichia coli</i>	ATCC 25922	>400	[33]
	Clinical isolate	>400	[33]
	K-12	500	[41]
	BW25113	400	[66]
	Clinical isolate	>200	[30]
	AG100	>1000	[42]
	ATCC 47004	250	[42]
	ATCC 35695	>512	[25]
	ATCC 13883	>400	[33]
	Clinical isolate	>400	[33]
<i>Klebsiella pneumoniae</i>	ATCC 13883	250	[42]
	ATCC 700721	>512	[25]
	ATCC 13311	>400	[33]
	ST329	500	[41]
<i>Salmonella enterica</i> serovar Typhimurium	ATCC 14028	>1000	[42]
	ATCC 27853	>400	[33]
	Clinical isolate	>400	[33]
<i>Pseudomonas aeruginosa</i>	ATCC 27853	342	[28]
	PAO1	1000	[41]
	Clinical isolate	>200	[30]
	PAO1	>1000	[42]
	PAO1	>1000	[71]
	PAO1	>512	[25]
	ATCC 43504	25	[35]
	ATCC 700392	50	[36]
<i>Helicobacter pylori</i>	ATCC 700824	50	[36]
	15 clinical isolates	25–100	[36]
	26 clinical isolates	37–1280 (MBC)	[37]
	LMG 10828	100	[21]
	AB36/11	100	[39]
<i>Arcobacter butzleri</i>	INSA776	100	[39]
	LMG 10829	50	[21]
	9 isolates	250–500 (MCC)	[46]
<i>Haemophilus ducreyi</i>	Clinical isolate	75	[30]
<i>Neisseria gonorrhoeae</i>	ATCC 13090	125	[30]
<i>Neisseria meningitidis</i>	MCV09	60	[38]
<i>Vibrio cholerae</i>	ATCC 10953	100	[52]
<i>Fusobacterium nucleatum</i>	225421	100	[39]
<i>Campylobacter jejuni</i>	873	50	[39]
<i>Campylobacter coli</i>			

(continued on next page)

Table 1 (continued)

Organism	Identifier	MIC (µg/mL) ^a	Reference
Fungi			
<i>Trichophyton mentagrophytes</i>	ATCC 18748	25–50	[28]
<i>Trichophyton tonsurans</i>	ATCC 28942	25–50	[28]
<i>Trichophyton rubrum</i>	ATCC 18762	25–50	[28]
<i>Epidermophyton floccosum</i>	ATCC 52066	25–50	[28]
<i>Microsporum gypseum</i>	ATCC 14683	25–50	[28]
<i>Candida albicans</i>	TIMM 1768	20	[29]
	Clinical isolate	>200	[30]
	ATCC 90028	>128	[31]
	ATCC 76615	>128	[31]
	SC5314	>300	[32]
<i>Saccharomyces cerevisiae</i>	KCTC 7296	10–20	[29]
<i>Botrytis cinerea</i>	SP1	60–140	[11]
<i>Trichosporon beigelii</i>	KCTC 7077	10	[29]

MIC, minimum inhibitory concentration; MBC, minimum bactericidal concentration;

MCC, minimum cidal concentration.

^a Data are the MIC unless otherwise stated.

wild-type [41], whilst an *acrB* mutant was eight-fold more susceptible to resveratrol [42]. Similarly, a *P. aeruginosa* mutant deficient in the MexAB–OprM efflux pump displayed two-fold greater susceptibility relative to the wild-type [41]. Use of the efflux pump inhibitor phenylalanine-arginine β -naphthylamide (PA β N) reduces the resveratrol MIC in *Arcobacter butzleri* and *A. cryaerophilus* by 16- and 4-fold, respectively [21]. Increased efficacy of resveratrol in the presence of PA β N has also been observed for *E. coli* and *Proteus mirabilis* [42].

The observation that inactivation of efflux pump function increases the inhibitory activity of resveratrol suggests that the antibacterial efficacy of resveratrol is partially attributed to interaction with cytoplasmic or periplasmic targets in Gram-negative bacteria.

4.4. Bacteriostatic or bactericidal effect of resveratrol

Time-kill curves have been used to determine whether the effect of resveratrol is bactericidal or bacteriostatic against several bacterial species. At 2–3 \times MIC, resveratrol is bacteriostatic against *Bacillus subtilis* [33], *S. aureus* [25,33], *E. faecalis* [33] and *Listeria monocytogenes* [44]. In contrast, resveratrol displays bactericidal activity against *Propionibacterium acnes* [45], *Haemophilus ducreyi* [46], *Campylobacter* spp. [39] and *Arcobacter* spp. [21,39]. Furthermore, resveratrol displays fungicidal activity against *C. albicans* [29].

5. Antivirulence properties

Virulence is the ability of a pathogen to cause disease in a host, and virulence factors are the mechanisms by which the pathogen causes damage to the host (e.g. by excretion of toxins) as well as mechanisms to establish an infection (e.g. factors for adhesion, invasion, colonisation and biofilm production) [47]. Expression of virulence genes is often tightly regulated for timely and co-ordinated adaptation to the environment, e.g. by quorum sensing (QS) or two-component systems (TCSs) [47]. The therapeutic applicability of antivirulence molecules concerns the rationale for disarming the pathogen of abilities to cause harm to the host and relying on the host immune system to eradicate the bacteria [48]. The antivirulence properties of resveratrol are highlighted in Table 2 and are outlined below.

5.1. Antibiofilm properties

Bacteria can live as planktonic cells or in aggregates attached to surfaces, referred to as biofilms. In biofilms, bacteria produce

an extracellular material in which the cells are embedded [49]. The advantage of biofilm formation by bacteria is the establishment of a more stable environment in order to provide protection against environmental challenges, including phagocytosis and antimicrobial agents [50]. Biofilm formation is a clinically important issue as it is associated with chronic and recurrent infections [51].

Resveratrol has been studied on various bacterial pathogens for its ability to reduce biofilm formation. For the Gram-negative anaerobic bacterium *Fusobacterium nucleatum*, which is implicated in dental plaque, resveratrol inhibits biofilm formation at concentrations (4–64-fold below the MIC) that do not affect the growth of planktonic cells [52]. Furthermore, resveratrol displays antibiofilm properties against the Gram-negative pathogens *V. cholerae* at concentrations 2–6-fold below the MIC [38] and *E. coli* [53] as well as against the Gram-positive bacterium *P. acnes* [54]. In *E. coli*, the effect is mediated by reduced expression of genes (*csgA* and *csgB*) encoding for curli production, which are important for biofilm formation [53]. For the Gram-positive pathogen *S. aureus*, resveratrol inhibits biofilm formation at a concentration 3–4-fold below the MIC, and in combination with vancomycin resveratrol displays a strong effect in eradicating established biofilms [55]. In contrast, in two other studies resveratrol did not reduce biofilm formation in *S. aureus* [56,57], indicating that testing conditions and strain variation may influence the impact.

5.2. Antimotility properties

For several bacterial species, motility is important in the colonisation stage [58]. Motility can occur, for example, via swimming and swarming, which require production of functional flagella and twitching that require type IV pili [59].

At subinhibitory concentrations of resveratrol, *P. mirabilis* displays reduced swarming ability in a dose-dependent manner [60]. Suppression of swarming in the presence of resveratrol is dependent on the TCS protein RsbA, which is a negative regulator of swarming [60]. Resveratrol reduces swimming and swarming in *E. coli* through downregulation of several motility and flagella genes [53]. Reduced swarming ability has also been reported for *Vibrio vulnificus* [61].

5.3. Toxin interference

Bacterial pathogens secrete a multitude of structurally and functionally different toxins and they are often highly important in the development of disease [47]. Interestingly, a few reports

Table 2
Antivirulence properties of resveratrol.

Virulence factor	Effect and organism	Concentration (µg/mL)	Reference
Biofilm	Reduction in biofilm production by <i>Fusobacterium nucleatum</i>	1.5625–25	[52]
	Reduction in biofilm production by <i>Escherichia coli</i>	50–100	[53]
	Reduction in biofilm production by <i>Propionibacterium acnes</i>		[54]
	Reduction in biofilm production by <i>Vibrio cholerae</i>	10–30	[38]
	Reduction in biofilm production by <i>Staphylococcus aureus</i>	100–150	[55]
	No reduction in biofilm formation by <i>S. aureus</i>	20–100	[57]
	No reduction in biofilm formation by <i>S. aureus</i>	100	[56]
	Reduction in biofilm production by <i>Burkholderia</i> spp.	25 µM	[65]
	Reduction in biofilm production by <i>Arcobacter butzleri</i> and <i>Campylobacter</i> spp.	12.5–50	[39]
Motility	Reduction in biofilm production by <i>Listeria monocytogenes</i>	50–100	[44]
	Reduction in swarming by <i>E. coli</i>	20	[53]
	Reduction in swarming by <i>Proteus mirabilis</i>	15–60	[60]
	Reduction in swarming by <i>Vibrio vulnificus</i>	30 µM	[61]
Quorum sensing (QS)	Reduction in QS by <i>Yersinia enterocolitica</i>	10–20	[64]
	Reduction in QS by <i>Burkholderia</i> spp.	25 µM	[65]
Toxins	Reduced haemolysis by <i>P. mirabilis</i>	30–60	[60]
	Reduced haemolysis by <i>S. aureus</i>	20	[57]
	Reduced haemolysis by <i>S. aureus</i>	10–100	[56]
	Reduced toxin expression by <i>V. vulnificus</i>	10–30 µM	[61]
	Suppressed toxin activity by <i>V. cholerae</i>	300–400 µM	[62]
Adhesion	Reduced adhesion to host cells by <i>V. vulnificus</i>	10–30 µM	[61]
Colonisation	Decreased urease activity by <i>Helicobacter pylori</i>	6.25–400	[36]

indicate that resveratrol in some cases interferes with toxin expression. In *V. vulnificus*, RtxA1 is a multifunctional cytotoxic toxin important for lethality in mice, and resveratrol treatment reduces *rtxA1* expression [61]. In *V. cholerae*, resveratrol inhibits cholera toxin (CT) endocytosis into host cells and directly binds CT and hence may potentially inhibit CT-induced diarrhoea [62]. Resveratrol also greatly inhibits haemolysis of human blood cells by *S. aureus*, but the mechanism of inhibition remains unknown [56,57].

5.4. Interference with quorum sensing (QS)

QS systems enable bacteria to respond to cell density and, through cell–cell communication, to regulate gene expression. In bacterial pathogens, QS often controls virulence gene expression allowing a co-ordinated attack that may overwhelm host defences [63]. QS involves the production and release of signal molecules, called autoinducers, that increase as a function of cell density. A threshold limit of the autoinducer is detected by the bacteria, leading to alterations in gene expression [63]. In *Yersinia enterocolitica* and *Erwinia carotovora*, resveratrol inhibits synthesis of the autoinducers *N*-acyl-homoserine lactones at a concentration that does not affect growth parameters [64]. Resveratrol also interferes with QS systems in *E. coli* and *Chromobacterium violaceum* through an uncharacterised mechanism [65].

Taken together, resveratrol affects multiple virulence traits at concentrations up to 64-fold below growth-inhibitory concentrations. Whether resveratrol may have any applications as an antivirulence compound needs to be assessed in suitable animal models.

6. Resveratrol in combination with conventional antimicrobials

In addition to working as an antimicrobial compound by itself, resveratrol has also been investigated for potential effects in combination with conventional antibiotics. In *E. coli*, resveratrol (at 0.5 × MIC) antagonises the bactericidal activity of ciprofloxacin, kanamycin, oxolinic acid and moxifloxacin, whereas oxacillin lethality is unaffected [66]. For *S. aureus*, resveratrol antagonises the lethal activity of daptomycin, moxifloxacin and oxacillin [66] and levofloxacin [67]. The mechanism of antagonism

is suggested to involve a reduction in reactive oxygen species (ROS) by resveratrol [66], which has antioxidant properties and thus protects macromolecules against damage by ROS [68]. Generation of ROS has been implicated as contributing to the lethality of bactericidal antibiotics [69] and, by scavenging ROS, resveratrol may suppress the bacterial killing with the mentioned antibiotics [66].

In contrast, resveratrol (at 0.5 × MIC) potentiates the efficacy of aminoglycosides approximately 16-fold against *S. aureus* and to a lesser extent against other Gram-positive pathogens such as *Staphylococcus epidermidis*, *Enterococcus faecium* and *E. faecalis* [25]. The mechanism of potentiation has been hypothesised to occur via inhibition of ATP synthase [25], as inactivation of genes encoding ATP synthase in *S. aureus* also sensitises this pathogen to aminoglycosides [70]. Furthermore, resveratrol enhances aminoglycoside activity against biofilms produced by *P. aeruginosa*, however the combinations of resveratrol and four different aminoglycosides did not display synergy on planktonic cells [71].

Taken together, resveratrol interferes with the inhibitory activity of different classes of antibiotics. Whether these effects are also evident in animal models remain to be explored.

7. In vivo antimicrobial activity of resveratrol

Several studies in humans have demonstrated that resveratrol displays high absorption yet low bioavailability of unchanged resveratrol following oral administration [72,73]. Resveratrol is readily metabolised following oral administration, with sulfate- and glucuronide-resveratrol conjugates reaching 3–8-fold higher plasma concentrations than free resveratrol [73]. Following oral administration of 5 g of *trans*-resveratrol as a single dose, the peak plasma level of resveratrol was 539 ng/mL at 1.5 h after administration and the mean plasma concentration was approximately 52 ng/mL at 24 h after administration [73]. Similarly, oral administration of 1 g of resveratrol resulted in an average 73 ng/mL of resveratrol in plasma after 1 h [74]. The low bioavailability of orally administered resveratrol limits this route of administration for potential systemic use of resveratrol for the treatment of bacterial infections, considering the inhibitory concentrations needed. Given that there is rapid turnover of resveratrol in humans and that higher plasma concentrations of resveratrol conjugates are observed compared with the non-modified compound, it could be interesting

to investigate the antimicrobial properties of such conjugates. Intravenous (i.v.) administration of resveratrol has also been investigated in humans, however the administered dose was low (0.2 mg) and resveratrol was still quickly metabolised [72], indicating that i.v. administration of resveratrol may also have limited, if any, antimicrobial applications for systemic infections. Finally, topical administration of resveratrol may still potentially enable the use of concentrations with a beneficial effect against different infectious diseases.

A few studies have investigated the therapeutic application of resveratrol against infectious diseases in animal models or human trials. The bacterium *P. acnes* is a contributing factor in the pathogenesis of acne vulgaris, one of the most common skin diseases [75]. In a human study, acne vulgaris patients treated with resveratrol (at a concentration of 1 mg/g of final preparation) experienced a significant reduction in facial acne lesions compared with treatment with the vehicle alone. Whether the therapeutic effect of resveratrol on acne vulgaris is a result of antimicrobial or anti-inflammatory properties was not elucidated in the study [76]. In contrast, in a study of experimental periodontitis in rats, continuous use of resveratrol did not promote any beneficial effect in reducing important oral periodontopathic bacteria [77]. Furthermore, topical application of resveratrol reduces lesion formation on the skin of mice by herpes simplex virus [78] and reduces replication of herpes simplex virus in the vagina of mice [79].

More studies are required to elucidate the potential of topical administration of resveratrol for the control of bacterial and fungal skin diseases, potentially in combination with conventional antimicrobials.

8. Conclusion

Resveratrol has gained significant scientific and public interest owing to acclaimed health-beneficial effects [1]. Substantial work conducted in vitro and in various animal models has documented potential benefits to human health following administration of resveratrol, however such benefits still remain to be documented in human clinical phase 3 trials [80]. Although clinical evidence for the acclaimed health benefits is largely lacking [1,80], resveratrol has still gained significant market traction as a dietary supplement [81]. In a recent survey, 18% of respondents in the USA had used resveratrol supplements, whereas only 3% had used them in Denmark [81].

In addition to the potential effects of resveratrol on various diseases, e.g. cancer, the compound also displays antimicrobial properties against bacterial, fungal and viral pathogens. As detailed in this review, resveratrol can inhibit bacterial and fungal growth, alter the expression of virulence factors, reduce biofilm formation, reduce motility and affect the susceptibility of bacteria to various classes of conventional antibiotics (Tables 1 and 2). However, the antimicrobial properties of resveratrol displayed in vitro are all at higher concentrations than have currently been achieved in human plasma following oral administration [72]. The low bioavailability of orally administered resveratrol limits this route of administration for systemic use of resveratrol for the treatment of bacterial and fungal infections [73]. However, it is currently not known whether metabolised resveratrol conjugates retain antimicrobial activity. If resveratrol conjugates retain antimicrobial activity, the plasma concentrations of effective resveratrol and derivatives may potentially be higher than currently expected.

An avenue for exploration of resveratrol as an antimicrobial agent is via topical administration, where higher concentrations of resveratrol are achievable. One human study demonstrated a positive effect on lesion reduction in acne vulgaris, however it is not known whether this effect is due to antibacterial properties against *P. acnes* [76]. The field of in vivo antimicrobial efficacy of

resveratrol remains largely unexplored, and future studies are warranted to elucidate antimicrobial efficacy following topical administration to treat various skin infections. Furthermore, resveratrol interacts with the efficacy of certain classes of conventional antibiotics and this may be needed to be taken into consideration during antibiotic regimen design [25,66]. Resveratrol potentiates the efficacy of aminoglycosides against several Gram-positive pathogens, and combinations should be tested in vivo for enhanced treatment efficacy [25]. Therefore, it will be interesting to investigate in animal models whether resveratrol can have any applicability as a potentiator for aminoglycosides. In contrast, the implication of resveratrol consumption as a dietary supplement could also potentially reduce the efficacy of certain antibiotic classes such as fluoroquinolones [66,67], which requires further investigations in animal models. As with so many other antimicrobial compounds, problems with resistance may arise and, as an example, enzymatic inactivation of resveratrol has been demonstrated [82]. Investigations in suitable animal models are greatly needed to assess the clinical potential of resveratrol as monotherapy or in combination with conventional antibiotics.

Funding

This work was supported by The Independent Research Fund Denmark [no. 12-127417] and by DNRF-120 to HI. The funding source had no influence on study design, data analysis or the decision to submit the article for publication.

Competing interests

None declared.

Ethical approval

Not required.

References

- [1] Tomé-Carneiro J, Larrosa M, González-Sarriás A, Tomas-Barberan FA, Garcia-Conesa MT, Espin JC. Resveratrol and clinical trials: the crossroad from in vitro studies to human evidence. *Curr Pharm Des* 2013;19:6064–93.
- [2] Renaud S, de Lorgeril M. Wine, alcohol, platelets, and the French paradox for coronary heart disease. *Lancet* 1992;339:1523–6.
- [3] Catalgol B, Batirel S, Taga Y, Ozer NK. Resveratrol: French paradox revisited. *Front Pharmacol* 2012;3:141.
- [4] Neves A, Lucio M, Lima J, Reis S. Resveratrol in medicinal chemistry: a critical review of its pharmacokinetics, drug-delivery, and membrane interactions. *Curr Med Chem* 2012;19:1663–81.
- [5] Marques FZ, Markus MA, Morris BJ. Resveratrol: cellular actions of a potent natural chemical that confers a diversity of health benefits. *Int J Biochem Cell Biol* 2009;41:2125–8.
- [6] Timmers S, Hesselink MK, Schrauwen P. Therapeutic potential of resveratrol in obesity and type 2 diabetes: new avenues for health benefits? *Ann N Y Acad Sci* 2013;1290:83–9.
- [7] Smoliga JM, Baur JA, Hausenblas HA. Resveratrol and health—a comprehensive review of human clinical trials. *Mol Nutr Food Res* 2011;55:1129–41.
- [8] Niesen DB, Hessler C, Seeram NP. Beyond resveratrol: a review of natural stilbenoids identified from 2009–2013. *J Berry Res* 2013;3:181–96.
- [9] Aggarwal BB, Bhardwaj A, Aggarwal RS, Seeram NP, Shishodia S, Takada Y. Role of resveratrol in prevention and therapy of cancer: preclinical and clinical studies. *Anticancer Res* 2004;24:2783–840.
- [10] Langcake P, Pryce R. The production of resveratrol by *Vitis vinifera* and other members of the Vitaceae as a response to infection or injury. *Physiol Plant Pathol* 1976;9:77–86.
- [11] Adrian M, Jeandet P, Veneau J, Weston LA, Bessis R. Biological activity of resveratrol, a stilbenic compound from grapevines, against *Botrytis cinerea*, the causal agent for gray mold. *J Chem Ecol* 1997;23:1689–702.
- [12] Soleas GJ, Diamandis EP, Goldberg DM. Resveratrol: a molecule whose time has come? And gone? *Clin Biochem* 1997;30:91–113.
- [13] Jeandet P, Bessis R, Sbaghi M, Meunier P. Production of the phytoalexin resveratrol by grapes as a response to *Botrytis* attack under natural conditions. *J Phytopathol* 1995;143:135–9.
- [14] Stervbo U, Vang O, Bonnesen C. A review of the content of the putative chemopreventive phytoalexin resveratrol in red wine. *Food Chem* 2007;101:449–57.

- [15] Cottart CH, Nivet-Antoine V, Laguillier-Morizot C, Beaudoux JL. Resveratrol bioavailability and toxicity in humans. *Mol Nutr Food Res* 2010;54:7–16.
- [16] Pervaiz S. Resveratrol: from grapevines to mammalian biology. *FASEB J* 2003;17:1975–85.
- [17] Britton RG, Kovoov C, Brown K. Direct molecular targets of resveratrol: identifying key interactions to unlock complex mechanisms. *Ann N Y Acad Sci* 2015;1348:124–33.
- [18] Gledhill JR, Montgomery MG, Leslie AG, Walker JE. Mechanism of inhibition of bovine F₁-ATPase by resveratrol and related polyphenols. *Proc Natl Acad Sci U S A* 2007;104:13632–7.
- [19] Dadi PK, Ahmad M, Ahmad Z. Inhibition of ATPase activity of *Escherichia coli* ATP synthase by polyphenols. *Int J Biol Macromol* 2009;45:72–9.
- [20] Hotra A, Suter M, Biuković G, Ragunathan P, Kundu S, Dick T, et al. Deletion of a unique loop in the magyobacterial F-ATP synthase γ subunit sheds light on its inhibitory role in ATP hydrolysis-driven H⁺ pumping. *FEBS J* 2016;283:1947–61.
- [21] Ferreira S, Silva F, Queiroz JA, Oleastro M, Domingues FC. Resveratrol against *Arcobacter butzleri* and *Arcobacter cryaerophilus*: activity and effect on cellular functions. *Int J Food Microbiol* 2014;180:62–8.
- [22] Boogerd FC, Boe L, Michelsen O, Jensen PR. *atp* mutants of *Escherichia coli* fail to grow on succinate due to a transport deficiency. *J Bacteriol* 1998;180:5855–9.
- [23] Hwang D, Lim Y-H. Resveratrol antibacterial activity against *Escherichia coli* is mediated by Z-ring formation inhibition via suppression of FtsZ expression. *Sci Rep* 2015;5:10029.
- [24] Subramanian M, Goswami M, Chakraborty S, Jawali N. Resveratrol induced inhibition of *Escherichia coli* proceeds via membrane oxidation and independent of diffusible reactive oxygen species generation. *Redox Biol* 2014;2:865–72.
- [25] Nöhr-Meldgaard K, Ovsepien A, Ingmer H, Vestergaard M. Resveratrol enhances the efficacy of aminoglycosides against *Staphylococcus aureus*. *Int J Antimicrob Agents* 2018;52:390–6.
- [26] Campagna M, Rivas C. Antiviral activity of resveratrol. *Biochem Soc Trans* 2010;38:50–3.
- [27] Abba Y, Hassim H, Hamzah H, Noordin MM. Antiviral activity of resveratrol against human and animal viruses. *Adv Virol* 2015;2015:184241.
- [28] Chan MM-Y. Antimicrobial effect of resveratrol on dermatophytes and bacterial pathogens of the skin. *Biochem Pharmacol* 2002;63:99–104.
- [29] Jung HJ, Hwang IA, Sung YS, Kang BS, Seu YB, et al. Fungicidal effect of resveratrol on human infectious fungi. *Arch Pharmacol Res* 2005;28:557–60.
- [30] Docherty JJ, Fu MM, Tsai M. Resveratrol selectively inhibits *Neisseria gonorrhoeae* and *Neisseria meningitidis*. *J Antimicrob Chemother* 2001;47:243–4.
- [31] Weber K, Schulz B, Ruhnke M. Resveratrol and its antifungal activity against *Candida* species. *Mycoses* 2011;54:30–3.
- [32] Houillé B, Papon N, Boudesocque L, Bourdeaud E, Besseau S, Courdavault V, et al. Antifungal activity of resveratrol derivatives against *Candida* species. *J Nat Prod* 2014;77:1658–62.
- [33] Paulo L, Ferreira S, Gallardo E, Queiroz JA, Domingues F. Antimicrobial activity and effects of resveratrol on human pathogenic bacteria. *World J Microbiol Biotechnol* 2010;26:1533–8.
- [34] Lechner D, Gibbons S, Bucar F. Plant phenolic compounds as ethidium bromide efflux inhibitors in *Mycobacterium smegmatis*. *J Antimicrob Chemother* 2008;62:345–8.
- [35] Mahady GB, Pendland SL. Resveratrol inhibits the growth of *Helicobacter pylori* in vitro. *Am J Gastroenterol* 2000;95:1849.
- [36] Paulo L, Oleastro M, Gallardo E, Queiroz JA, Domingues F. Anti-*Helicobacter pylori* and urease inhibitory activities of resveratrol and red wine. *Food Res Int* 2011;44:964–9.
- [37] Martini S, Bonechi C, Rossi C, Figura N. Increased susceptibility to resveratrol of *Helicobacter pylori* strains isolated from patients with gastric carcinoma. *J Nat Prod* 2011;74:2257–60.
- [38] Augustine N, Goel A, Sivakumar K, Kumar RA, Thomas S. Resveratrol—a potential inhibitor of biofilm formation in *Vibrio cholerae*. *Phytomedicine* 2014;21:286–9.
- [39] Duarte A, Alves AC, Ferreira S, Silva F, Domingues FC. Resveratrol inclusion complexes: antibacterial and anti-biofilm activity against *Campylobacter* spp. and *Arcobacter butzleri*. *Food Res Int* 2015;77:244–50.
- [40] Sun D, Hurdle JG, Lee R, Lee R, Cushman M, Pezzuto JM. Evaluation of flavonoid and resveratrol chemical libraries reveals abyssinone II as a promising antibacterial lead. *ChemMedChem* 2012;7:1541–5.
- [41] Tegos G, Stermitz FR, Lomovskaya O, Lewis K. Multidrug pump inhibitors uncover remarkable activity of plant antimicrobials. *Antimicrob Agents Chemother* 2002;46:3133–41.
- [42] Jung CM, Heinze TM, Schnackenberg LK, Mullis LB, Elkins SA, Elkins CA, et al. Interaction of dietary resveratrol with animal-associated bacteria. *FEMS Microbiol Lett* 2009;297:266–73.
- [43] Piddock LJ. Multidrug-resistance efflux pumps—not just for resistance. *Nat Rev Microbiol* 2006;4:629.
- [44] Ferreira S, Domingues F. The antimicrobial action of resveratrol against *Listeria monocytogenes* in food-based models and its antibiofilm properties. *J Sci Food Agric* 2016;96:4531–5.
- [45] Docherty JJ, McEwen HA, Sweet TJ, Bailey E, Booth TD. Resveratrol inhibition of *Propionibacterium acnes*. *J Antimicrob Chemother* 2007;59:1182–4.
- [46] Nawrocki EM, Bedell HW, Humphreys TL. Resveratrol is cidal to both classes of *Haemophilus ducreyi*. *Int J Antimicrob Agents* 2013;41:477–9.
- [47] Rasko DA, Sperandio V. Anti-virulence strategies to combat bacteria-mediated disease. *Nat Rev Drug Discov* 2010;9:117–28.
- [48] Clatworthy AE, Pierson E, Hung DT. Targeting virulence: a new paradigm for antimicrobial therapy. *Nat Chem Biol* 2007;3:541–8.
- [49] Flemming H-C, Wingender J. The biofilm matrix. *Nat Rev Microbiol* 2010;8:623–33.
- [50] Hall-Stoodley L, Costerton JW, Stoodley P. Bacterial biofilms: from the natural environment to infectious diseases. *Nat Rev Microbiol* 2004;2:95–108.
- [51] Costerton JW, Stewart PS, Greenberg EP. Bacterial biofilms: a common cause of persistent infections. *Science* 1999;284:1318–22.
- [52] He Z, Huang Z, Zhou W, Tang Z, Ma R, Liang J. Anti-biofilm activities from resveratrol against *Fusobacterium nucleatum*. *Front Microbiol* 2016;7:1065.
- [53] Lee J-H, Cho HS, Joo SW, Chandra Regmi S, Kim J-A, Ryu C-M, et al. Diverse plant extracts and trans-resveratrol inhibit biofilm formation and swarming of *Escherichia coli* O157: H7. *Biofouling* 2013;29:1189–203.
- [54] Coenye T, Brackman G, Rigole P, De Witte E, Honraet K, Rossel B, et al. Eradication of *Propionibacterium acnes* biofilms by plant extracts and putative identification of icariin, resveratrol and salidroside as active compounds. *Phytomedicine* 2012;19:409–12.
- [55] Qin N, Tan X, Jiao Y, Liu L, Zhao W, Yang S, et al. RNA-Seq-based transcriptome analysis of methicillin-resistant *Staphylococcus aureus* biofilm inhibition by ursolic acid and resveratrol. *Sci Rep* 2014;4:5467.
- [56] Lee K, Lee J-H, Ryu SY, Cho MH, Lee J. Stilbenes reduce *Staphylococcus aureus* hemolysis, biofilm formation, and virulence. *Foodborne Pathog Dis* 2014;11:710–17.
- [57] Cho HS, Lee J-H, Cho MH, Lee J. Red wines and flavonoids diminish *Staphylococcus aureus* virulence with anti-biofilm and anti-hemolytic activities. *Biofouling* 2015;31:1–11.
- [58] Josenhans C, Suerbaum S. The role of motility as a virulence factor in bacteria. *Int J Med Microbiol* 2002;291:605–14.
- [59] Harshey RM. Bacterial motility on a surface: many ways to a common goal. *Annu Rev Microbiol* 2003;57:249–73.
- [60] Wang W-B, Lai H-C, Hsueh P-R, Chiou RY-Y, Lin S-B, Liaw S-J. Inhibition of swarming and virulence factor expression in *Proteus mirabilis* by resveratrol. *J Med Microbiol* 2006;55:1313–21.
- [61] Kim JR, Cha MH, Oh D-R, Oh WK, Rhee JH, Kim YR. Resveratrol modulates RTX toxin-induced cytotoxicity through interference in adhesion and toxin production. *Eur J Pharmacol* 2010;642:163–8.
- [62] Morinaga N, Yahiro K, Noda M. Resveratrol, a natural polyphenolic compound, inhibits cholera toxin-induced cyclic AMP accumulation in Vero cells. *Toxicol* 2010;56:29–35.
- [63] Miller MB, Bassler BL. Quorum sensing in bacteria. *Annu Rev Microbiol* 2001;55:165–99.
- [64] Truchado P, Tomás-Barberán FA, Larrosa M, Allende A. Food phytochemicals as quorum sensing inhibitors reducing production and/or degrading autoinducers of *Yersinia enterocolitica* and *Erwinia carotovora*. *Food Control* 2012;24:78–85.
- [65] Brackman G, Hillaert U, Van Calenbergh S, Nelis HJ, Coenye T. Use of quorum sensing inhibitors to interfere with biofilm formation and development in *Burkholderia multivorans* and *Burkholderia cenocepacia*. *Res Microbiol* 2009;160:144–51.
- [66] Liu Y, Zhou J, Qu Y, Yang X, Shi G, Wang X, et al. Resveratrol antagonizes antimicrobial lethality and stimulates recovery of bacterial mutants. *PLoS One* 2016;11:e0153023.
- [67] Tosato MG, Schilardi P, de Mele MFL, Thomas AH, Miñan A, Lorente C. Resveratrol enhancement of *Staphylococcus aureus* survival under levofloxacin and photodynamic treatments. *Int J Antimicrob Agents* 2018;51:255–9.
- [68] Leonard SS, Xia C, Jiang B-H, Stinefelt B, Klandorf H, Harris GK, et al. Resveratrol scavenges reactive oxygen species and effects radical-induced cellular responses. *Biochem Biophys Res Commun* 2003;309:1017–26.
- [69] Dwyer DJ, Collins JJ, Walker GC. Unraveling the physiological complexities of antibiotic lethality. *Annu Rev Pharmacol Toxicol* 2015;55:313–32.
- [70] Vestergaard M, Leng B, Haaber J, Bojer MS, Vegge CS, Ingmer H. Genome-wide identification of antimicrobial intrinsic resistance determinants in *Staphylococcus aureus*. *Front Microbiol* 2016;7:2018.
- [71] Zhou J-W, Chen T-T, Tan X-J, Sheng J-Y, Jia A-Q. Can the quorum-sensing inhibitor resveratrol function as an aminoglycoside antibiotic accelerant against *Pseudomonas aeruginosa*? *Int J Antimicrob Agents* 2018;52:35–41.
- [72] Walle T, Hsieh F, DeLegge MH, Oatis JE, Walle UK. High absorption but very low bioavailability of oral resveratrol in humans. *Drug Metab Dispos* 2004;32:1377–82.
- [73] Boockch DJ, Faust GE, Patel KR, Schinas AM, Brown VA, Ducharme MP, et al. Phase I dose escalation pharmacokinetic study in healthy volunteers of resveratrol, a potential cancer chemopreventive agent. *Cancer Epidemiol Biomarkers Prev* 2007;16:1246–52.
- [74] Chow HS, Garland LL, Hsu C-H, Vining DR, Chew WM, Miller JA, et al. Resveratrol modulates drug- and carcinogen-metabolizing enzymes in a healthy volunteer study. *Cancer Prev Res (Phila)* 2010;3:1168–75.
- [75] Perry A, Lambert P. *Propionibacterium acnes*: infection beyond the skin. *Expert Rev Anti Infect Ther* 2011;9:1149–56.
- [76] Fabbrocini G, Staibano S, De Rosa G, Battimelli V, Fardella N, Iardi G, et al. Resveratrol-containing gel for the treatment of acne vulgaris. *Am J Clin Dermatol* 2011;12:133–41.
- [77] Cirano FR, Casarin RCV, Ribeiro FV, Casati MZ, Pimentel SP, Taiete T, et al. Effect of resveratrol on periodontal pathogens during experimental periodontitis in rats. *Braz Oral Res* 2016;30:e128.

- [78] Docherty JJ, Smith JS, Fu MM, Stoner T, Booth T. Effect of topically applied resveratrol on cutaneous herpes simplex virus infections in hairless mice. *Antiviral Res* 2004;61:19–26.
- [79] Docherty JJ, Fu MM, Hah JM, Sweet TJ, Faith SA, Booth T. Effect of resveratrol on herpes simplex virus vaginal infection in the mouse. *Antiviral Res* 2005;67:155–62.
- [80] Berman AY, Motechin RA, Wiesenfeld MY, Holz MK. The therapeutic potential of resveratrol: a review of clinical trials. *NPJ Precis Oncol* 2017;1:35.
- [81] Aschemann-Witzel J, Grunert KG. Resveratrol food supplements: a survey on the role of individual consumer characteristics in predicting the attitudes and adoption intentions of US American and Danish respondents. *BMC Public Health* 2015;15:110.
- [82] McAndrew RP, Sathitsuksanoh N, Mbughuni MM, Heins RA, Pereira JH, George A, et al. Structure and mechanism of NOV1, a resveratrol-cleaving dioxygenase. *Proc Natl Acad Sci U S A* 2016;113:14324–9.